CHOICE OF MANAGEMENT IN PATIENTS WITH THYROTOXICOSIS*

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THE course of thyrotoxicosis is characteristically chronic and it sometimes threatens life. It is not always continuously progressive as it may be interrupted by relatively brief remissions which occur independently of therapeutic measures. Occasionally, without treatment, there may be a complete and permanent disappearance of all active manifestations of the disease. In general, however, it may be stated that once the disorder is established, the chance of a spontaneous recovery is remote. With the use of the various types of modern therapy, the possibility of a cure is great. The purpose of this presentation is to evaluate the relative merits of the several forms of treatment and to discuss their possible shortcomings.

In discussing the choice of management, the following must be considered: first, subtotal thyroidectomy; second, various antithyroid drugs; third, radioactive iodine. The use of iodine alone as a definitive form of therapy cannot be recommended because it rarely if ever produces a permanent cure although long periods of improvement may follow its use. Certainly it is of great value as a preoperative procedure, and it is an essential agent in the control of a thyroid "crisis." Roentgen-ray therapy may produce some benefit in many patients with thyrotoxicosis but a complete cure is rare, and if irradiation is to be employed it has been demonstrated that radioactive iodine is far superior. There remain for discussion, therefore, subtotal thyroidectomy, antithyroid drugs, and radioactive iodine. No other forms of treatment can be considered as having sufficient value to merit discussion.

TREATMENT OF TOXIC ADENOMA

In patients with toxic adenoma, the course of the disease is highly typical and differs importantly from that observed in exophthalmic goiter. It usually progresses gradually until the patient is often com-

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pletely incapacitated, frequently as a result of cardiac complications. Remissions are rare, but thyroid "storms" are unlikely. Favorable responses to iodine and the antithyroid drugs, and radioactive iodine therapy do occur but usually they are less striking than in patients with Graves's disease. On the other hand, the response of patients with toxic adenomas to subtotal thyroidectomy is uniformly satisfactory. Additional indications which make surgical therapy advisable in such patients are the presence of an unsightly goiter, symptoms arising from pressure on the trachea, and the possibility of the development of carcinoma of the thyroid gland which occurs in about 3 to 5 per cent of all patients with toxic adenomas.

The optimum treatment in such patients, therefore, for the reasons given, is subtotal thyroidectomy performed under the proper circumstances. With the elimination of the useless thyroid artery ligation, the preservation of the parathyroid glands and their blood supply, the knowledge that a truly subtotal thyroidectomy must be done, the improvement in surgical technique, and the effective preoperative use of iodine and propylthiouracil, the surgical treatment of toxic goiter has reached a high degree of perfection. Sometimes, however, on account of the patient's age, cardiac status, or because surgical treatment is refused, some other form of therapy must be employed. In such patients, I would use radioactive iodine in suitable dosage but would anticipate that the results would be somewhat less satisfactory than in patients with exophthalmic goiter. If the required facilities are not available for this form of treatment, then I would administer propylthiouracil in combination with iodine. With this medication the anticipated results likewise are less satisfactory than in patients with diffuse hyperplastic goiter.

In the presence of symptoms resulting from pressure on the trachea, relief is usually not accomplished without operative treatment. Hence this should be advised if the condition is of a serious extent, but only after the proper preoperative treatment with iodine and propylthiouracil has been effective. This is indicated by the patient's satisfactory general condition by a reduction in the basal metabolic rate to +15 or less, and the complete control of any congestive heart failure which may be present. Fortunately, with improvement in preoperative and postoperative care and in surgical technique, along with the likelihood of reducing the basal metabolic rate to normal before surgery is attempted, thyroidectomy can be carried out safely in a high proportion of patients who have

been regarded previously as serious risks on account of their age or damage of the cardiovascular system.

Treatment of Exophthalmic Goiter

At present, also, subtotal thyroidectomy must be considered to be the optimum treatment of patients with exophthalmic goiter although it is my opinion that in the near future radioactive iodine may prove to be superior. In patients with exophthalmic goiter, however, the results of subtotal thyroidectomy while usually satisfactory are less so than in those with toxic adenoma. This mainly for three reasons: 1) the intensity of the thyrotoxicosis is frequently greater than in toxic adenoma, and hence the operative risk is increased; 2) the possibility of cure is less, as a recurrence is more likely; and 3) if exophthalmos is present, it may actually be accentuated by the operation.

The results of subtotal thyroidectomy as reported by Vander Laan and Swenson[1] in 130 patients with diffuse toxic goiter (exophthalmic goiter), operated upon at the Peter Bent Brigham Hospital in Boston between the years 1933 and 1940, are representative of those obtained in other hospitals with excellent surgical facilities in that period. They report that in 87 per cent the results were satisfactory although included in this group were 13.9 per cent of the patients in whom temporary hypothyroidism was observed, and in 2.3 and 1.5 per cent respectively temporary unilateral vocal cord paralysis and transient tetany occurred. An unsatisfactory result was reported in 13 per cent of the patients of whom 3.5 per cent had persistent or recurrent thyrotoxicosis, 0.8 per cent permanent parathyroprivia, 0.8 per cent vocal cord paralysis, and in 8.1 per cent death occurred postoperatively.

Hence it must be taken into account that when a subtotal thyroidectomy is performed with its attendant discomfort and hospitalization cost, a certain unavoidable risk is incurred which may lead to death or a distressing and permanent disability. It is true that in some hospitals the results are better than those observed by Vander Laan and Swenson but in many others the record is even less favorable. It should be kept in mind, however, that since these results have been reported, the almost universal preoperative use of antithyroid drugs has made the operation safer.

In my experience, permanent myxedema developing after a subtotal thyroidectomy is a rarity, unless the patient has previously been treated

with radioactive iodine. In a few patients there may be a period of several months following the operation in which the basal metabolic rate is lowered to the vicinity of −20 or −25 per cent and the blood cholesterol is higher than 300 milligrams per 100 cc. in association with mild clinical evidences of myxedema. Such patients should not be treated with desiccated thyroid, however, but kept under observation. In all whom I have observed, these values have returned to normal and the symptoms of hypothyroidism disappeared spontaneously within a few months. This probably occurs when the remnant of thyroid tissue left by the surgeon undergoes a sufficient degree of hyperplasia to supply the normal amount of thyroxine for the body needs.

Undoubtedly temporary, and in rare instances, permanent parathyroprivia, will occur in the experience of any surgeon despite his ability if he operates upon a sufficient number of patients with Graves's disease. Hypoparathyroidism probably results in most instances because there is either inadvertent surgical interference with the blood supply of the parathyroid glands, or sometimes when the operation is done on a patient in whom there are less than the normal number of these glands. While permanent hypoparathyroidism is a serious and distressing complication, nevertheless with the aid of parathyroid hormone, high vitamin D ingestion, dihydrotachysterol (AT_{10}) and an increased calcium intake, the condition can be controlled with a reasonable degree of efficiency.

There will always be a small percentage of patients who suffer from a permanent postoperative vocal cord paralysis and a number of postoperative deaths. With the use of the proper preoperative procedures, the fatalities have had a gratifying decrease in incidence. The rule should be enforced strictly, however, that a subtotal thyroidectomy should never be performed on a patient with a toxic goiter unless the basal metabolic rate is +15 or less. If this cannot be accomplished with iodine and propylthiouracil, then the patient should be treated with radioactive iodine. From our experience, the use of propylthiouracil in combination with iodine always results in a reduction of the basal metabolic rate to normal limits unless 1) the patient is under severe psychic stress; 2) there is an infection which produces a febrile reaction; and 3) the patient is not taking the prescribed medication and may not be cooperating with the proper rest and other reasonable hygienic measures. Such patients should be admitted to the hospital to be placed at bed rest and given propylthiouracil treatment under careful supervision.

My recommendations, therefore, concerning the treatment of patients with exophthalmic goiter are *first*, for the present at least, that a subtotal thyroidectomy be done by a competent surgeon, experienced in this field of operative surgery. This should be performed after the patient's basal metabolic rate has been reduced to +15 or lower by the proper preoperative use of propylthiouracil and iodine. If the basal metabolic rate cannot be lowered satisfactorily, then treatment with radioactive iodine should be considered. If a thyroidectomy is done at a time when the basal metabolic rate is still elevated, it must be recognized that although the operation will probably be successful there is a small but definite added risk incurred under these circumstances. The chances of a cure by surgery are good but there is always the possibility of a recurrence. If this occurs, the use of radioactive iodine is advised. Furthermore, it appears to be likely that in the near future, with further experience and when radioactive iodine is generally available, it may supersede surgery as the treatment of choice. This is because it appears to be fairly certain in producing a permanent cure, it spares the patient the expense and discomfort of an operation, and the risk is negligible.

The Use of Antithyroid Drugs

With the introduction of the antithyroid drugs into clinical medicine by Astwood in 1943,[2] a new and valuable therapeutic agent in the treatment of thyrotoxicosis was made available. In the intervening nine years, an ample opportunity has been afforded to determine their mode of action, evaluate their usefulness in the management of toxic thyroid conditions, determine their untoward effects, and conclude the most satisfactory one of several preparations to be used.

It is believed that the effect of antithyroid drugs is to interfere with the synthesis of thyroxine in the thyroid gland. This is thought to be accomplished by the inhibition of the action of an enzyme in the thyroid gland which converts iodide into free iodine. As the latter is the only type of iodine that can unite with tyrosine to form thyroxine, the process is blocked at this stage. When an antithyroid drug is given, therefore, the formation of thyroxine is partially or completely prevented. The amount of this hormone which is present in the gland is then gradually utilized by the body. When this is reduced, there will be a diminution in the basal metabolic rate to approximately normal. Also, it is known that with a decrease in the thyroxine of the circulating blood,

there is a resultant activation of the anterior pituitary gland to secrete an excessive amount of the thyroid stimulating hormone which in turn eventually causes a hypertrophy and hyperplasia of the thyroid acinar cells.

By means of antithyroid drugs, therefore, the basal metabolic rate can be brought to +15 per cent or less in practically every patient. Furthermore, it is known that the undesirable effect due to hyperplasia and hypertrophy of the acinar cells, can be eliminated by the simultaneous administration of iodine which causes the gland to revert to the resting or colloid state. This beneficial influence is greater than that of iodine alone which usually causes the basal metabolic rate to fall to approximately +20 or +25 and remain there usually for only a month or two despite a continuation of the medication. A basal metabolic rate thus lowered with iodine alone is promptly increased again, sometimes within a few days, when the medication is omitted.

Many antithyroid drugs of the thiouracil type have been introduced into medicine. In my experience, however, on the basis of effectiveness and its comparative non-toxic effect, propylthiouracil in a dosage of 100 milligrams t.i.d. with the simultaneous administration of 4 drops of Lugol's solution daily should be given to all patients, regardless of the estimated toxicity of the thyrotoxicosis, who are to undergo a subtotal thyroidectomy. I have over the years observed thyroid surgery done without any type of preparation, since 1923 with the preoperative use of iodine only, and since 1943 with iodine and thiouracil combined. As a result of these latter two innovations in preoperative treatment, I have seen the operative mortality diminished from 5 per cent or more, to 1.0 per cent; and now, in the hands of the experienced surgeon, to approximately 0.1 per cent. Never, without exception, would I advise a subtotal thyroidectomy in the presence of an elevated basal metabolic rate. This is because the added risk, while small, is unnecessary and should be eliminated.

With this combination of propylthiouracil and iodine, in a great majority of patients, the basal metabolic rate diminishes approximately from 0.5 to 1.0 per cent per day. If a patient does not require hospitalization for cardiovascular complications or other reasons, preoperative medication may be given at home and arrangements made for admission to the hospital at a time when it is anticipated that the basal metabolic rate will be normal.

It is recognized that propylthiouracil may cause certain untoward effects occasionally. They are less likely to occur, however, with this antithyroid drug than with any other preparation. The important but rare complications of treatment are agranulocytosis, skin rashes, a febrile reaction and, in extremely rare instances, hypoprothrombinemia. After an extensive experience with all types of antithyroid preparations, including the more toxic ones such as thiouracil, I have never observed a fatality following this form of treatment, although a number of patients have been extremely ill with agranulocytosis when the latter drug was used. The only precaution which must be taken, and one which must be thoroughly understood by both the patient and physician is this: it is emphasized to the patient that the drug prescribed may occasionally cause undesirable symptoms, usually characterized by chills, fever, sore throat and skin rash. If these occur, or any other important complication arises, then the medication should be discontinued immediately and the patient advised to consult his physician, and have a leukocyte count and the differential white blood cell count done. By so doing, our results have been entirely satisfactory. The routine periodic estimations of the total white blood cell count have not proved satisfactory in my experience because they may give a false sense of security. This is because the leukocyte count may decrease from normal to an extremely low level within a few hours. The observation and heeding of significant symptoms is simpler and even more efficient.

It has not been possible to produce a decrease in the basal metabolic rate to below +20 per cent in a small percentage of ambulatory patients. This has never occurred, however, in my experience, when the patient has been in the hospital under observation. The causes of such an unsatisfactory result previously stated, have been failure to take the medication as prescribed, powerful psychic influences such as distressing and persistent marital differences, inadequate rest, excessive coffee consumption, or some other obvious contributing influence. The desired effect on the basal metabolic rate has been attained when these causes have been corrected.

In a few patients, the toxic effects of the drug, such as a skin rash, have made it necessary to discontinue it permanently. When agranulocytosis due to *thiouracil* has developed, this drug has been resumed within a week or ten days after recovery, and continued for long periods without a recurrence except in one patient. If such a serious complica-

tion should occur, it is better judgment, however, to discontinue all antithyroid drugs and treat the thyrotoxicosis with radioactive iodine. In one such patient in whom propylthiouracil was omitted on account of a skin rash and a subtotal thyroidectomy performed when the basal metabolic rate was still elevated, death resulted from the only postoperative thyroid "storm" I have seen in some years.

After it had been demonstrated that the thiouracil group of drugs combined with iodine medication was effective, it was hoped that a remission thus induced might be prolonged and this therapy, therefore, be employed as a form of medical treatment. It is true that a majority of patients, especially those of the younger age group, with only a slight enlargement of the thyroid gland and a mild thyrotoxicosis, will have a prolonged remission following the administration of antithyroid drugs and iodine. This is more likely to be accomplished if the medication is continued for eight to twelve months and the basal metabolic rate kept at a normal level for that period. With the discontinuance of the medication, the patients frequently remain in good health, without any manifestations of thyroid disorder for a period of ten to twelve months or more. The threat of a recurrence is always present, however, and the thyroid gland may remain prominent and be a source of complaint. In my opinion, therefore, propylthiouracil and iodine should not be employed as a medical form of treatment of exophthalmic goiter or toxic adenoma unless the patient refuses operation and radioactive iodine is not available. Furthermore, I do not recommend it as a definitive form of therapy in patients whose physical status does not warrant a subtotal thyroidectomy but only as a temporary expedient prior to the use of radioactive iodine or surgical removal of a major portion of the gland.

The fact that thiouracil and allied compounds are known to block the formation of the thyroid hormone raises the point that possible harm to the infant in utero might follow the use of such drugs during pregnancy. Theoretically it is possible that a thyroid deficiency might develop in the fetus and premature birth occur or cretinism be present at birth. Observations on the largest series of patients with pregnancy and thyrotoxicosis have been reported by Bell[3] who also summarizes the previous literature. He concludes that satisfactory results, especially in the early months of pregnancy, can be attained with little risk to the pregnant patient when subtotal thyroidectomy is done following adequate preparation with propylthiouracil and iodine. Full term living infants

born of such patients have been entirely normal. There is an added risk, however, to the infant in utero as he reports a fetal loss of 33 per cent. It is not clear, however, whether this is due to the thyrotoxicosis or to the administration of the antithyroid drug.

His report does indicate that patients with hyperthyroidism can be given an antithyroid drug and operated upon successfully during the first five months of pregnancy with good results as far as the mother is concerned. In his opinion, the condition is probably best treated during the last trimester of pregnancy by antithyroid drugs until some time after delivery when subtotal thyroidectomy can be performed. He emphasized the fact that after the sixth month, pregnancy causes an increase in the basal metabolic rate to +20 or +25 and suggested that lowered rates may be avoided by the administration of desiccated thyroid as this may be a contributing factor to fetal mortality. I cannot vouch for the efficacy of such medication from first-hand experience.

Treatment With Radioactive Iodine

With the discovery of induced radioactivity in 1934 and the preparation of radioactive isotopes of iodine in the same year by Fermi, the treatment with radioactive iodine became possible. In 1942 both Hertz and Roberts[4] and Hamilton and Lawrence[5] published the first reports on the use of radioactive iodine with favorable results in the treatment of thyrotoxicosis. In 1946 Chapman and Evans[6] confirmed these conclusions and demonstrated by biopsy that following such treatment there resulted an extensive fibrosis of the thyroid gland with an obvious curtailment of functional hyperactivity.

Since these observations, a comparatively large number of patients with exophthalmic goiter and toxic adenoma have been subjected to this form of treatment. From a review of the published cases and my own personal experience in association with Dr. William H. Beierwaltes, it appears that this therapeutic agent can now be accepted as satisfactory in its effects and one which will be regarded with increasing favor in the future.

It is my opinion that patients with thyrotoxicosis due either to exophthalmic goiter or to toxic adenoma should be treated with radioactive iodine 1) if they refuse operation or their condition is such that a subtotal thyroidectomy would threaten life; 2) if a previous subtotal thyroidectomy has been unsuccessful; 3) if there is severe exophthalmos and

it is feared that a subtotal thyroidectomy might increase this condition; 4) if surgical treatment is refused. Furthermore, I believe it is permissible to say that it will eventually be the treatment of choice, at least in patients with exophthalmic goiter. This is because it appears to be highly effective and subtotal thyroidectomy is less certain in its effects in this condition than in toxic adenoma.

With a widening experience, it appears that a single dose of radioactive iodine (I^{131}) will produce a satisfactory lowering of the basal metabolic rate and control other manifestations of thyrotoxicosis in a high percentage of patients. Judging from our own experience and from the results of the many cases reported in the literature, it appears that the medication will produce a remission in over 90 per cent of the patients. Such a remission appears to be permanent in most instances. Further observations of a large number of patients over a long period of time is necessary, however, before any conclusions can be drawn concerning the long range effect of such treatment. There is no reason known at present which would indicate that the effects of radioactive iodine will not be permanent.

In a few patients of our group it has been necessary to give a second and sometimes a third dose, but it is not advisable to repeat the medication until a period of at least three months has elapsed. This is because experience has shown that although almost all of the radiation has been delivered to the thyroid gland in the first fourteen days after administration, the anatomical changes which it has initiated may continue progressively for a period of at least three months.

When the control of thyrotoxicosis is observed after the simple procedure of administering one-half glass of water containing a few micrograms of potassium iodide in which the iodide isotope is radioactive, it is impressive as compared to the cost, discomfort and apprehension associated with a thyroidectomy. Furthermore, the complications such as parathyroid tetany, paralysis of the vocal cords, a fatal termination and probably progressive exophthalmos are not observed following the use of radioactive iodine. With the great prospect of cure and unlikely occurrence of unfavorable effects it is easy to understand why this form of therapy may ultimately be the one of choice in all types of thyrotoxicosis if there are no pressure symptoms from the goiter or unless it should be removed for cosmetic reasons.

Possible Complications of Radioactive Iodine Therapy: The chief

problems incident to the use of radioactive iodine, aside from the lack of availability and technical matters relative to handling the product, are concerned with 1) the uncertainty of the dose; 2) the possibility of producing myxedema; and 3) the threat of causing malignancy of the thyroid gland.

The difficulty in dosage seems to be concerned chiefly with the following: 1) previous and recent administration of iodine; 2) the size of the gland; and 3) the severity of the thyrotoxicosis. The thyroid gland may not take up the desired amount of radioactive iodine because of previous medication. All patients who are to be treated with I^{131} should discontinue iodine before the medication is given in order to prevent this inhibiting influence. Just how long such abstinence should be required is uncertain but in practice it has usually been for ten days to two weeks. It is also advisable to discontinue the use of all antithyroid drugs for a period of two days prior to the administration of the medication. Either one or both of these drugs can be administered within twelve to twenty-four hours after the radioactive material is given without completely nullifying the effect of radioactive iodine. It is probable that the I^{131} would have a more complete effect if they were withheld for ten days to two weeks. It appears obvious that despite our uncertainty regarding the relation of iodine and propylthiouracil medication to the efficacy of treatment with I^{131}, they must not play an important role in preventing the action of radioactive iodine, if these precautions are taken, because the results have been so satisfactory in a high percentage of patients. One point which should be kept in mind is that if a patient displays even mild premonitory symptoms of a thyroid crisis, a more favorable time should be awaited to give the radioactive material, as the necessary discontinuance of the iodine at such a time might threaten to precipitate such a condition.

Unquestionably the weight of the thyroid gland plays an important part in determining the size of an effective dose. It is known that patients with toxic adenoma and large glands show more resistance to treatment than patients with smaller glands. That this may be true in patients with exophthalmic goiter as well is demonstrated by four patients reported by Skillern, McCullage and Hays[7] who found that in four patients with glands weighing between 75 and 200 grams each, it was necessary to give a dosage between 65 and 92 millicuries. It is their belief that these relatively large doses were required on account of the increased weights of

the glands. Consequently, it is their opinion that an initial dose of 20 to 25 millicuries is indicated in patients with large diffuse glands of Graves's disease. It is their experience, a total dose of 50 millicuries has never been required in patients in whom a diffuse toxic goiter was estimated to weigh less than 75 grams.

It has also been determined that there is an inverse relationship between the intensity of the thyrotoxicosis and the size of the dose of radioactive iodine. In other words, if there is a mild hyperthyroidism, the dose should be large, and if the condition is more intense, it should be smaller. This is probably related to the capacity of the gland to take up the iodine as it is generally considered that the avidity of the thyroid epithelium for iodine is directly proportional to the severity of the thyrotoxicosis.

The possibility of producing myxedema with radioactive iodine must be considered when this treatment is given to any patient. It should be emphasized, however, that it does not occur commonly, and, when present, it should not be regarded as a major misfortune. The latter statement receives support because when such a complication does result, it means that the patient will never be troubled with thyrotoxicosis again. Furthermore, with the aid of a small dose of desiccated thyroid daily, the patient may be maintained in perfect condition for the remaining normal span of life as far as thyroid function is concerned. It should be kept in mind that although myxedema may develop occasionally from excessive treatment with radioactive iodine alone, it is more likely to occur when a thyroidectomy is done after the patient has received prior therapy with this medication. This is assumed to result from a failure of the remnant of the thyroid gland to undergo compensatory hyperplasia after the subtotal thyroidectomy has been performed.

The possibility that radioactive iodine might have a carcinogenic effect on the thyroid gland is mentioned by all observers who have had experience with this form of medication. This is based, however, solely on theoretical considerations as not one single case of malignancy has been proven to be due to this agent to date. Furthermore, I do not know of cancer developing in the thyroid gland following intensive irradiation with the roentgen irradiation. While such a possibility must still be considered when radioactive material is employed in the treatment of thyrotoxicosis, the likelihood of its occurrence is remote. It should also be kept in mind that only a portion, perhaps 50 to 80 per cent of the admin-

istered radioactive iodine, is retained by the thyroid gland, and the remaining portion is excreted through the kidneys. There is no evidence that this has produced harmful effects on these organs in patients with thyrotoxicosis, or following the administration of much larger doses employed in the treatment of cancer of the thyroid gland.

Treatment of Malignant Exophthalmos

The treatment of malignant exophthalmos continues to be a problem which is not completely solved although much can be done for patients with this complication. In my experience, the hazard of exophthalmos and the level of the basal metabolic rate appear to bear an inverse ratio to each other in many instances. That is, patients with thyrotoxicosis and prominent protrusion of the eyes who have a relatively low or normal basal metabolic rate, are faced with a greater risk of accentuating the condition by subtotal thyroidectomy than those with exophthalmos and a high basal metabolic rate. Preliminary impressions suggest, however, that when thyrotoxicosis is treated with radioactive iodine, the possibility of increasing the exophthalmos is much less than following subtotal thyroidectomy. Hence in patients with exophthalmos in whom the basal metabolic rate is elevated, I believe preference should be given to treatment with radioactive iodine.

The greatest problem is encountered in patients with pronounced exophthalmos and a normal or only slightly elevated basal metabolic rate. This is because there may be a progressive change following subtotal thyroidectomy, which in some instances leads to loss of the orbits. Theoretically, and substantiated to a considerable extent by practical experience, it is to be expected that the performance of a subtotal thyroidectomy will lead to an accentuation of the exophthalmos. This is thought to occur because following such an operation the thyroxine of the circulating blood is lowered. Such a change activates the anterior pituitary gland to produce more of the thyrotropic hormone which increases the degree of exophthalmos.

In patients with a normal or an almost normal basal metabolic rate, therefore, I believe that treatment with subtotal thyroidectomy, radioactive iodine or with any of the antithyroid drugs is contraindicated because the malignant exophthalmos may be increased. I first treat such patients with desiccated thyroid gland orally in doses of 0.1 to 0.13 grams daily and Lugol's solution 0.3 cc. daily. Probably less than 10 per

cent, however, are helped with this form of therapy. Such patients should be kept under strict observation to detect possible progression of the exophthalmos and especially for two ominous signs, namely, corneal ulceration and the inability to close the eyes during sleep. They are an indication for prompt and more radical therapeutic measures in order to avert loss of the eyes. In the first place all measures should be taken to protect the orbits. If there is edema of the lids and corneal ulceration, then tarsorrhaphy should be performed, the patient should be placed in a sitting position in bed, an 800 milligram low sodium diet given, and ammonium chloride in doses of 3.0 grams t.i.d. administered. Preliminary observations indicate that cortisone, 50 milligrams four times daily, given orally, is helpful. In a considerable number of patients my associate, Dr. William H. Beierwaltes, has administered roentgen-ray therapy in doses of 750 r to two temporal ports with promising results,[8] and he is now testing the effect of twice that dosage in another group of patients. No important untoward effects of this treatment have been observed. In my opinion, its use is justified, if the exophthalmos resists other forms of therapy and certainly if there is danger of losing the eyes. It is possible that some or all of the good results achieved by this form of therapy are due to the action of the roentgen rays on the retro-orbital tissues.

If all other measures fail, and the danger to the eyes is great, then orbital decompression as advocated by Naffziger[9] should be employed.

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